Max Costa, Ph.D., Professor and Chairman
Department of Environmental Medicine
NYU School of Medicine
57 Old Forge Road
Tuxedo, NY 10987
Telephone: (845) 731-3515 Fax: (845) 351-2118
E-mail: costam@env.med.nyu.ed

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RE: NTP technical report on the Toxicology and Carcinogenesis study of Styrene-Acrylonitrile Trimer in F344/rats

To Whom it may Concern:

I have been asked by Dow Chemical Company to read the draft report referenced above and offer my opinion and interpretation of the results of the three studies that are reported in this document. The seven week study was conducted to establish a toxiciy dose range for the other two studies (18 week and two year study) The seven week study found that the 4000 ppm dose in the feed was too high so that the other studies used 1600 ppm as the highest dose. Suprisingly only one male rat died 3 days after weaning at this 4000 ppm dose. These rats were exposed to these doses during gestation which is considered the most susceptible period for toxicity, but there was no evidence of teratogenic effects. Exposure during embryonic development is one of the most sensitive tests of toxicity and many common drugs such as aspirin exhibit teratogenic activity in experimental animals.

The cleanup standard for this chemical in groundwater in Toms River has been 15 parts per trillion since it was suspected of being highly toxic and carcinogenic. However the results of the 18 week toxicity study and the 2 year carcinogenicity study demonstrated that this compound was not toxic and carcinogenic. In fact in the 2 year study animals exposed at the higher doses had a lower incidence of pituitary gland adenoma, mononuclear cell leukemia in male and female rats and a lower incidence of mammary gland fibroadenoma in females. In the longer studies(18 weeks and 2 year) animal given the higher doses had lower weights, yet except for an initial period of less feed consumption (4-6 weeks) they adjusted to the taste of SAN –Trimer and ate equivalent amount as the control. This may be due to a protective effect against cancer of caloric restriction during early life.

In all of the studies pregant rats were exposed to the SAN-Trimer from day 7 of gestation and this chemical is known to cross the placenta and get into mother's milk. Trans-generational carcinogenesis is the most senstive way to detect a potentially carcinogenic substances yet there was very little effect from in utero exposure and thus little risk of fetal basis of adult disease. For

example another chemical such as arsenite did not induce tumors in rats until they were exposed in utero.

All the in vitro tests demonstrated that it was not mutagenic or clastogenic. However the in vivo DNA damage tests such as the comet assay and micronuclei indicated some activity. Comet assays are generally done with lymphocytes and it is very experimental to perform these assays with brain or liver cells. In fact an examination of Table C2 shows a very modest response in lymphocytes that was not dose related in females. (male, Control=3.3, 37.5 mg/kg= 2.6, 75=3.1, 150=3.7, 300=4.3, female Control=6.2, 37.5 mg/kg=5.1, 75mg/kg=6.2,150mg/kg=7.6 and300mg/kg=7.0) The positive control gave a response of 30 or greate for males and females. The Brain and Liver cells had a much higher background indicating that there may be endogenous DNA damage during the isolation of these cells. In addition there were no increase in neoplasms in liver, brain or in blood cells. Generally in vivo tests are less senstive than in vitro tests. It should also be noted that the toxicity of SAN-Trimer appeared to decrease when exposed to S9 microsomes indicating metabolic inactivation. Thus it is hard to understand the higher effects in vivo and no effects in vitro. It also has a short life in vivo (3.5 hrs)

In summary the results of this study which administered SAN-Trimer at high doses did not find that it was toxic or carcinogenic, even when rats were exposed in utero.

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Max Costa